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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Paper No. 36

Application/Control Number: 08/644,289  
Art Unit: 1642

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Application Number: 08/644,289

Filing Date: May 10, 1996

Appellant(s): KULESZ-MARTIN, MOLLY F.

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Michael Dunn

For Appellant

### **EXAMINER'S ANSWER**

This is in response to the appeal brief filed 08/15/03.

**(1) *Real Party in Interest***

A statement identifying the real party in interest is contained in the brief.

**(2) *Related Appeals and Interferences***

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A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

**(3) Status of Claims**

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 1, 3-6, 8-11, 17-18.

The 112, first paragraph, written description of claims 15-16, 19 is withdrawn. Claims 15-16, 19 are free of prior art and are now allowable.

Claims 12-14 are withdrawn from consideration as not directed to the elected invention.

Claims 2, 7 have been canceled.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

No amendment after final has been filed.

**(5) Summary of Invention**

The summary of invention contained in the brief is correct.

**(6) Issues**

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows:

The 112, first paragraph, written description of claims 15-16, 19 is withdrawn.

Claims 15-16, 19 are free of prior art and are now allowable.

**(7) *Grouping of Claims***

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the claims are not drawn to patentably distinct inventions, and have been subjected to the same or related art rejections.

**(8) *Claims Appealed***

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(9) *Prior Art of Record***

Han et al, "Alternative spliced p53 RNA in transformed and normal cells of different tissue types." Nucleic acid Res, vol. 20, no. 8 (April 25, 1992), pp. 1979-1981.

Sambrook et al (eds). Molecular Cloning, A laboratory Manual. Second edition, ((Cold Spring Harbor laboratory Press. 1989(, p.17.2.

Hupp et al. "Regulation of the specific DNA binding function of p53". Cell, vol.71 (November 27, 1992), pp.875-886.

Funk et al. "A transcriptionally active DNA-binding site for human p53 protein complexes". Molecular and Cell Biology, vol.12, no.6 (June 1992), pp.2866-2871.

EP, A1, 0 529 160 LEE et al 03-03-93.

**(10) *Grounds of Rejection***

The following ground(s) of rejection are applicable to the appealed claims:

**REJECTION UNDER 35 USC 103**

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I. Claims 1, 3-4, 17 are rejected under 35 USC 103 as being obvious over Han et al, in view of Sambrook et al, Hupp et al, and Funk et al.

Claims 1, 3-4 are drawn to a plasmid containing a cDNA sequence which encodes a protein designated p53as. Said p53as is sequentially the same as wild type p53 up to the final 50 carboxy terminal amino acids of p53. Said p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus. Said negative regulatory domain must be activated in p53 for p53 to have active DNA binding. Said p53as and activated p53 bind to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT", SEQ ID NO:5. Said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53. Said p53as naturally occurs in a mammal or is a mouse p53as. Claim 17 is drawn to a cell transfected with said plasmid.

Han et al teach making of cDNAs from alternatively spliced p53 RNA in transformed and normal murine epidermal cells, using reverse transcriptase. Han et al further teach using polymerase chain reaction, and specific primers to amplify fragments from said cDNA, which are cloned into plasmids for sequencing. Han et al also teach that sequence analysis of the plasmids show regions representing regularly spliced wild type p53, and alternative splicing at the 3' end of intron 10. The alternatively spliced species AS-p53 are predicted to result in premature termination of p53 protein, making it 9 amino acid shorter and differing in 25 amino acids at the C-terminus. Otherwise, the

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molecule is identical to wild type p53 (See the abstract, p.1980, column 2, last paragraph to p.1981, column 1, first paragraph and third paragraph). Han et al further teach that the carboxy terminus of the protein translated from AS-p53 is predicted to be quite distinct from the wild type R-p53 by having reduced basic charges, which could influence the secondary structure of p53 (p. 1981, first column, last paragraph). In addition Han et al teach that the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes and that more precise biochemical and **biological characterization** (emphasis added) of AS-p53 protein along with R-p53 protein appear to be critical in **future studies of p53 function** (emphasis added) in normal cells and in oncogenesis. (p. 1981, first column, last paragraph bridging second column, first paragraph).

Han et al do not teach a plasmid containing full length p53as cDNA, and a cell transformed with said plasmid. Han et al do not teach that p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus. Han et al do not teach that said negative regulatory domain must be activated in p53 for p53 to have active DNA binding, and that said p53as and activated p53 bind to the same p53 DNA binding sequence "AGGCATGCCT/AGGCATGCCT" (SEQ ID NO:5). Han et al do not teach that said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53.

Sambrook et al teach that expressing large amounts of proteins from cloned genes in plasmids is an art standard technique, and is valuable to the purification, localization, and functional analysis of the proteins. Sambrook et al also teach intact native proteins have been produced in large amount in *E. Coli* for functional studies (p. 17.2, lines 10-11). That is a host cell, i.e. *E. Coli*, transfected with a plasmid for expressing intact proteins is taught by Sambrook et al. Sambrook et al further teach that cloned genes are conventionally expressed using expression vectors and that expression of cloned proteins have been used to: (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein; (2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in various cell types; (4) to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins (para bridging pages 16.3 and 16.4).

Thus, not only do Sambrook et al teach the technical feasibility of a reasonable expectation of success, Sambrook et al teach a motivation to do so, i.e. to obtain large quantities of intact, native protein for investigation of function of the protein.

Hupp et al teach that it is the C-terminus that inhibits DNA binding of wild type p53, and that removal of the 30 C-terminal amino acids constitutively activates p53, suggesting that this region plays a regulatory role in controlling p53 activity (p.876, first column, first paragraph, p. 878, second column, last paragraph). Hupp et al teach that altering the conformation of the C-terminal amino acid motif or removal of the C-terminal

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domain or binding of a monoclonal antibody specific for C-terminus of p53 would activate p53 DNA binding (p. 881, first column, second paragraph). Hupp et al also teach a consensus DNA binding site for p53 (p.884, first column, third paragraph under "synthesis of oligonucleotide and preparation of duplex substrates").

Funk et al teach a DNA binding site for human p53, i.e. the repeated TGCCT motif, or the half-sites TGCCC and TGTCC (p.2870, first column, first paragraph, last 5 lines).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to clone a full length p53as cDNA into plasmid for the following reasons:

1) To study function of a protein, i.e. p53 and AS-p53, as suggested by Han et al, and Sambrook et al, it is art standard to incorporate a full length polynucleotide sequence into a plasmid to express and obtain a full length or intact native protein, as taught by Sambrook et al, because it is well known in the art that fragments of a protein usually would not have biological activity, as evidenced by Sambrook et al, who teach that for functional study, large amount of **intact native protein** (emphasis added) are produced. Furthermore, the full length p53as protein could be readily obtained by routine techniques of cloning and expressing a plasmid containing a full length cDNA, for producing intact native protein, as taught by Sambrook et al, and

2) The existence of a full length p53as cDNA is known from the teaching of Han et al, because Han et al teach its predicted protein, as being prematurely terminated as compared to p53 protein, and having 9 amino acid shorter and differing in 25 amino

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acids at the C-terminus, as compared to p53 protein. Furthermore, although Han et al do not directly teach the structure of a full length p53as cDNA, one of ordinary skill in the art could readily obtain it, in view of the available information concerning the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA, as taught by Han et al. The protein produced by the alternative spliced RNA of p53 taught by Han et al seems to be same the claimed p53as sequence, i.e., being different from the wild type p53 within the final 50 carboxy-terminal amino acids so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, wherein said negative regulatory domain must be activated in p53 or p53 to have active DNA binding, because, as evidenced by Hupp et al, it is the C-terminus that inhibits DNA binding of wild type p53, and removal of the 30 C-terminal amino acids or change in the conformation of the C-terminus would activate p53 DNA binding, suggesting that this region plays a regulatory role in controlling p53 activity. Further, in view of the teaching by Hupp et al and Han et al, one would have expected that the AS-p53 taught by Han et al would have a different conformation at the C-terminus, and thus would be activated to bind to DNA, such as the DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" (SEQ ID NO:5), which contains the repeated motif TGCCT bound by activated wild type p53, as taught by Funk et al. In addition, one would have expected that the 25 C-terminal amino acids of the AS-p53 protein taught by Han et al would elicit an antibody which is specific for AS-p53 but not with p53, because said 25 C-terminal amino acids are different from the C-terminal amino acids of the wild type p53, as taught by Han et al.

The reference does not specifically teach that p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, wherein said negative regulatory domain must be activated in p53 for p53 to have active DNA binding, said p53as and activated p53 binding to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" (SEQ ID NO:5) , and said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53. However, the claimed cDNA sequence encoding p53as appears to be the same as the prior art cDNA sequence encoding AS-p53, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

The motivation is as follows: To obtain full length, i.e. intact, native protein, such as full length p53as, expressed by plasmid containing full length cDNA **for studying function** of the protein, as suggested as Sambrook et al, or for studying biological characterization of the protein, as suggested by Han et al. Further, since the differences

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in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes, it is critical to include p53as in the study of the function of p53, as suggested by Han et al.

II. Claims 5-6, 8-11, 18 are rejected under 35 USC 103(a) as being unpatentable over Han et al, in view of Lee et al.

Claims 5-6, 8-11 are drawn to a viral vector containing a cDNA sequence which encodes a protein designated p53as. Said p53as is sequentially the same as wild type p53 up to the final 50 carboxy terminal amino acids of p53. Said p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus. Said negative regulatory domain must be activated in p53 for p53 to have active DNA binding. Said p53as and activated p53 bind to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT", SEQ ID NO:5. Said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53. Said p53as naturally occurs in a mammal or is a mouse p53as. Said viral vector is a baculovirus vector. Claim 18 is drawn to a cell transfected with said viral vector.

The teaching of Han et al has been set forth above.

Han et al do not teach a viral vector containing full length p53as cDNA and a cell transformed with said viral vector.

Lee et al teach the use of baculovirus vectors delivered into insect cells to produce large quantities of protein. Lee et al further teach the importance and advantages of a mechanism to obtain intact, biochemically active protein in large quantities to advance investigation of the properties of said protein (p.2, lines 40-45).

Thus not only do Lee et al teach the technical feasibility of a reasonable expectation of success, Lee et al teach a motivation to do so, i.e. to obtain large quantities of intact, biochemically active protein for investigation of the properties of the protein.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the baculovirus vector system of Lee et al, with a reasonable expectation of success, as a vector for expressing tumor suppressor protein, such as the full length alternatively spliced p53 cDNA, which could be readily obtained, in view of the available information taught by Han et al, i.e. the alternative spliced site on wild type p53, the primer unique for p53as, and the source for RNA for the alternatively spliced RNA.

The protein produced by alternative spliced RNA of p53 taught by Han et al seems to be same the claimed p53as sequence, i.e., being different from the wild type p53 within the final 50 carboxy-terminal amino acids so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, wherein said negative regulatory domain must be activated in p53 for p53 to have active DNA binding, said p53as and activated p53 bind to DNA, such as the DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" (SEQ ID NO:5),

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*supra*. In addition, one would have expected that the 25 C-terminal amino acids of the AS-p53 protein taught by Han et al would elicit an antibody which is specific for AS-p53 but not with p53, because said 25 C-terminal amino acids are different from the C-terminal amino acids of the wild type p53, as taught by Han et al.

The reference does not specifically teach that p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, wherein said negative regulatory domain must be activated in p53 for p53 to have active DNA binding, said p53as and activated p53 binding to the same p53 DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" (SEQ ID NO:5) , and said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53. However, the claimed cDNA sequence encoding p53as appears to be the same as the prior art cDNA sequence encoding AS-p53, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

The motivation is to obtain full length, i.e. intact, biochemically active protein sequence, such as full length p53as, to study the properties of the protein, as suggested by Lee et al, or for studying biological characterization of the protein, as suggested by Han et al. Further, since the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes, it is critical to include p53as in the study of the function of p53, as suggested by Han et al.

**(11) *Response to Argument***

**REJECTION UNDER 35 USC 103**

I. Claims 1, 3-4, 17 remain rejected under 35 USC 103 as being obvious over Han et al, in view of Sambrook et al, Hupp et al, and Funk et al for reasons already of record.

Appellant argues that Han et al do not teach incorporation of a full length p53as sequence into a plasmid and that the suggestion to look for incorporation of a full length p53as sequence into a plasmid is merely from the statement in Han et al that "more precise biochemical and biological characterization of AS-p53 protein along with R-p53 protein appear to be critical in future studies of p53 function in normal cells and oncogenesis". Appellant argues that there are literally thousands of ways one might proceed with "more precise biochemical and biological characterization". Appellant further argues that since Han et al do not actually form any proteins at all, formation of proteins based upon the disclosure of Han et al, with respect to p53as was speculative. Appellant asserts that whether or not the sequence containing inhibitors that prevent transcription or translation was not known, disclosed or suggested by Han et al.

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Appellant further asserts that it is classic hindsight to zeroing in on incorporation of a complete p53as cDNA sequence into a plasmid as a way to proceed with "biochemical and biological characterization" without any other such suggestion in Han et al.

Appellant argues that Sambrook et al generally discuss production and characterization of proteins, but makes no suggestion as to any specific proteins and certainly not p53as protein. Appellant asserts that if one were to follow the logic of the Examiner, all future plasmids containing **novel** (emphasis added) DNA sequence would be unpatentable. Appellant argues that there needs to be some suggestion or reason in the art for incorporating a particular sequence into a plasmid or other vector to even want to do characterization of any protein that might result. Appellant argues that neither Han et al, nor Sambrook et al give any suggestion why one would want to incorporate a complete p53as into a plasmid from among myriads of other ways that one might proceed with characterization of p53as.

Appellant argues that in the present case, one would not even know whether the p53as alternatively spliced cDNA could be transcribed and then translated into protein until it was tried. Obvious to try would not be obviousness.

Appellant asserts that the teaching of Hupp et al and Funk does not cure these critical defects.

Appellant's arguments set forth above have been considered but are not deemed to be persuasive for the following reasons:

Contrary to Appellant's arguments, the expression of cloned sequences into proteins is conventional in the art. Sambrook et al clearly teach that expressing large

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amounts of proteins from cloned genes in plasmids is valuable to the purification, localization, and functional analysis of the proteins (p.17.2). Sambrook et al also teach that intact native proteins have been produced in large amount in *E. Coli* for functional studies, and describe methods and plasmid vectors for producing fusion proteins and intact native proteins in bacteria (p. 17.2, p.17.10-17.28, 17.36). Sambrook et al further teach that cloned genes are conventionally expressed using expression vectors and that expression of cloned proteins have been used to: (1) confirm the identity of a cloned gene by using immunological or functional assays to detect the encoded protein; (2) produce large amounts of proteins of biological interest that are normally available in only limited quantities from natural sources; (3) to study the biosynthesis and intracellular transport of proteins following their expression in various cell types; (4) to elucidate structure-function relationships by analyzing the properties of normal and mutant proteins (para bridging pages 16.3 and 16.4).

Further, **the existence of a full length p53as cDNA is known from the teaching of Han et al**, because Han et al teach its predicted protein, as being prematurely terminated as compared to p53 protein, and having 9 amino acid shorter and differing in 25 amino acids at the C-terminus, as compared to p53 protein. Moreover, although Han et al do not directly teach the structure of a full length p53as cDNA, one of ordinary skill in the art could readily obtain it, in view of the available information concerning the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA, as taught by Han et al. Thus the alternative spliced p53as is readily transcribed into mRNAs which are used

by Han et al. The alternative spliced RNA of p53 taught by Han et al seems to be same the claimed p53as sequence, i.e., being different from the wild type p53 within the final 50 carboxy-terminal amino acids so as to lack a negative regulatory domain of p53 for p53 specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, wherein said negative regulatory domain must be activated in p53 or p53 to have active DNA binding, because, as evidenced by Hupp et al, it is the C-terminus that inhibits DNA binding of wild type p53, and removal of the 30 C-terminal amino acids or change in the conformation of the C-terminus would activate p53 DNA binding, suggesting that this region plays a regulatory role in controlling p53 activity. Further, in view of the teaching by Hupp et al and Han et al, one would have expected that the AS-p53 taught by Han et al would have a different conformation at the C-terminus, and thus would be activated to bind to DNA, such as the DNA binding sequence "AGGCATGCCT/ AGGCATGCCT" (SEQ ID NO:5), which contains the repeated motif TGCCT bound by activated wild type 53, as taught by Funk et al. In addition, one would have expected that the 25 C-terminal amino acids of the AS-p53 protein taught by Han et al would elicit an antibody which is specific for AS-p53 but not with p53, because said 25 C-terminal amino acids are different from the C-terminal amino acids of the wild type p53, as taught by Han et al.

Thus given the teaching of Han et al, that allows one to deduct the full length p53as sequence, and given the teaching of Sambrook et al concerning the expression of plasmid vectors containing genes of interest into intact native proteins, which is conventional, one would have expected that full length p53as sequence is readily transcribed and translated into proteins with a reasonable expectation with success.

The motivation is as follows: To obtain full length, i.e. intact, native protein, such as full length p53as, expressed by plasmid containing full length cDNA **for studying function** of the protein, as suggested as Sambrook et al, or for studying biological characterization of the protein, as suggested by Han et al. Further, since the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes, it is critical to include p53as in the study of the function of p53, as suggested by Han et al.

II. Claims 5-6, 8-11 and 18 remain rejected under 35 USC 103 as being obvious over Han et al in view of Lee et al for reasons already of record

Appellant argues that the rejection is a classic hindsight. Appellant argues that Han et al do not teach incorporation of a full p53as sequence into a plasmid, let alone into virus, and that there are literally thousands of ways one might proceed with “more precise biochemical and biological characterization of AS-p53 protein” taught by Han et al. Appellant argues that formation of proteins based on the disclosure of Han et al without any other suggestion is speculative, since Han et al did not actually form any proteins at all. Appellant asserts that whether or not the sequence contains inhibitors

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that prevent transcription or translation is not known, disclosed or suggested by Han et al.

Appellant argues that Lee et al makes no suggestion as to p53as, and is directed to incorporation of entirely different sequences into viruses for purposes unrelated to the function of p53as. Appellant asserts that Lee et al do not cure the defects of Han et al. Appellant asserts that if one were to follow the logic of the Examiner, all future viruses containing **novel** (emphasis added) DNA sequence would be unpatentable, because of the generic procedures of Lee et al. Appellant argues that there needs to be some suggestion or reason in the art for incorporating a particular sequence into a virus or other vector to even want to do characterization of any protein that might result. Appellant argues that neither Han et al, nor Lee et al give any suggestion why one would want to incorporate a complete p53as into a virus from among myriads of other ways that one might proceed with characterization of p53as.

Appellant argues that in the present case, one would not even know whether the p53as alternatively spliced cDNA could be transcribed and then translated into protein until it was tried. Obvious to try would not be obviousness.

Appellant's arguments set forth above have been considered but are not deemed to be persuasive for the following reasons:

It is noted that the expression of cloned sequences into proteins using viral vector is conventional in the art. Lee et al teach expression of a gene in baculovirus vectors to produce large quantities of protein, and the importance and advantages to obtain intact, biochemically active proteins in large quantities for the investigation of the

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properties of the proteins, by using viral vectors (p.2, lines 40-45). Thus, not only Lee et al teach the technical feasibility of a reasonable expectation of success, Lee et al also teach a motivation to do so, i.e. to obtain intact, biochemically active proteins in large quantities for the investigation of the properties of the proteins.

Further, the existence of a full length p53as cDNA is known from the teaching of Han et al, because Han et al teach its predicted protein, as being prematurely terminated as compared to p53 protein, and having 9 amino acid shorter and differing in 25 amino acids at the C-terminus, as compared to p53 protein. Moreover, although Han et al do not directly teach the structure of a full length p53as cDNA, one of ordinary skill in the art could readily obtained it, in view of the available information concerning the alternative spliced site on wild type p53, the primers unique for p53as, and the source of RNA for the alternatively spliced RNA, as taught by Han et al. Thus the alternative spliced p53as is readily transcribed into mRNAs which are used by Han et al. The alternative spliced RNA of p53 taught by Han et al seems to be same the claimed p53as sequence.

Thus given the teaching of Han et al, that allows one to deduct the full length p53as sequence, and given the teaching of Lee et al concerning expression of genes incorporated in a viral vector into intact native proteins, which is routine in the art, one would have expected that full length p53as sequence is readily transcribed and translated into proteins with a reasonable expectation with success.

The motivation is to obtain full length, i.e. intact, biochemically active protein, such as full length p53as, expressed by a vector containing full length p53as cDNA to

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study the properties of an expressed protein, as taught by Lee et al and for studying the function of p53as, since the differences in the carboxy terminus between AS-p53 and R-53 protein could lead to significant biochemical and biological changes and it is critical to include p53as in the study of the function of p53, as suggested by Han et al.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

MINH TAM DAVIS, PhD.

November 29, 2003

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